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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,324	07/13/2001	Shizuo Akira	31671-173143	2302

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/889,324	AKIRA ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, 12-51* is/are pending in the application.

4a) Of the above claim(s) *8,9 and 12-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☒ Claim(s) *5-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 12-51 are pending in the application. Claims 8, 9 and 12-51 are withdrawn from consideration for being directed to non-elected subject matter. Accordingly, claims 1-7 are currently under examination.

This Office Action is in response to the Amendment filed on 12/29/03.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/29/03 has been entered.

Response to Amendment

The rejection of claims 1-7 under 35 U.S.C.112 1st paragraph (written description) has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1-7 under 35 U.S.C. 112 1st paragraph (scope of the enablement) is maintained for reasons discussed below.

Claims 5-7 are objected to for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse comprising homozygous disruption of TLR4, TLR2 or MyD88 gene in its genome, wherein such disruption results in no production of endogenous TLR4, TLR2 or MyD88 protein, and exhibits the phenotype of unresponsive to bacterial cell components that is a lipoprotein or lipopeptide, does not reasonably provide enablement for a mouse comprising any type of disruption in said genes, including heterozygous disruption, wherein one functional copy of gene is present. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In response to this rejection, Applicants assert that the amended claims satisfy the enablement requirement.

This argument has been fully considered but deemed unpersuasive. The claimed invention encompasses both heterozygous and homozygous disruption in a mouse genome of its endogenous MyD88, TLR2 or TLR4 gene. Further, the claims also encompass a mouse comprising any type of disruption in the MyD88, TLR2 or TLR4 gene, including mutation and deletion, wherein decreased level of protein or a mutant protein is produced.

The phenotype of the transgenic animal is unpredictable. When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous MyD88, TLR2 and TLR4 knockout

mouse, wherein said mouse does not produce functional MyD88, TLR2 or TLR4 protein. The specification does not disclose mice that harbor other types of mutation or deletion that result in production of mutant protein or decreased level of functional protein that exhibit the same phenotype. The claims encompass heterozygotes, but since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. Thus, the phenotype of a mouse comprising any type of disruption in the MyD88, TLR2 or TLR4 gene is unpredictable. In addition, the phenotype of a heterozygous MyD88, TLR2 or TLR4 knockout mouse is also unpredictable. Thus, the specification, in the instant case, is not enabling for knockout mice that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. Therefore, the claimed invention is only enabled to the scope of a mouse comprising homozygous disruption of TLR4, TLR2 or MyD88 gene in its genome, wherein such disruption results in no production of endogenous TLR4, TLR2 or MyD88 protein, and exhibits the phenotype of unresponsive to bacterial cell components that is a lipoprotein or lipopeptide.

Claim Objections

Claims 5-7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5 recites the mouse model is unresponsive to endotoxin as a bacterial cell component by disruption of TLR4 gene. However, claim 1 recites a mouse model with disruption of TLR2 or MyD88 gene. Therefore, claim 5 fails to limit claim 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER